DECLARATION OF THOMAS D. MADDEN, PH.D.

I, Thomas D. Madden, Ph.D., declare as follows:

1. I currently hold the position of Senior Director, Technology Development & Licensing, at Inex Pharmaceuticals Corp. ("INEX"), located in Burnaby, British Columbia, Canada, an assignee of U.S. Patent Application No. 10/782,738, entitled "Compositions and Methods for Treating Lymphoma."

2. I have read and am familiar with the above-identified patent application and the Office Action mailed July 20, 2006 with respect to this application. In this Office Action, the Examiner alleges that the claimed kits are obvious over Webb (U.S. Patent No. 5,741,516), alone or in combination with Mehlhorn (U.S. Patent No. 5,762,957. I submit this Declaration further to a personal interview conducted with the Examiner on December 7, 2006, in order to provide additional evidence that the kits claimed in the instant application, which comprise three specific components that are combined to produce liposome-encapsulated vincristine, are not obvious in light of these references. In addition, I provide data discussed during the personal interview and requested by the Examiner, which demonstrates that vincristine is unstable in citrate buffer, even in the absence of liposomes.

3. As noted in my previous Declarations submitted May 23, 2006 and October 20, 2006, the fully loaded liposomal vincristine formulations disclosed in Webb, which are stated to provide stable drug retention in a chemically stable liposomal carrier, would appear to be an ideal product presentation. Unrecognized by Webb, however, the chemical stability of vincristine within the liposomal interior greatly limits the acceptable shelf-life for such a loaded formulation. Specifically, the levels of vincristine degradation products within the loaded liposomes exceed the USP requirements within less than 6 months of manufacture (Figure 1). Such a short shelf-life is unsuitable for a pharmaceutical product. Accordingly, the adoption of the claimed three-component kit format for loading prior to use is necessary, despite being less desirable from a

commercial and clinical perspective. Studies conducted by INEX confirm that the kit format for liposomal vincristine provides for a shelf-life of 2 years.

4. In addition, in response to the Examiner's inquiry in this regard, I provide data from experiments conducted at Inex, which demonstrate that vincristine is surprisingly unstable in citrate buffer even in the absence of liposomes. The stability of vincristine in citrate buffer at pH range 3.75 to 4.75 under various temperatures was investigated. These studies demonstrated that vincristine was most stable at a pH of about 4.5-4.7. However, the shelf-life of vincristine in citrate buffer, calculated from the observed pseudo first order rate constants, was less than 2 months even at 5° C (allowing 5% degradation), as shown in Table 1.

Table 1. Vincristine stability in citrate buffer at 5°C

Formulation	pH	$T_{1/2}$ (days)	$T_{5\%}$ (days)
Vincristine sulfate in 300 mM citrate buffer. $[vinc]_{initial}$ approx. 50mg/ml	3.96	187	13.9
	4.25	293	17.7
	4.49	231	17

Inclusion of mannitol (100 mg/ml) in the citrate buffer provided only a modest increase in vincristine stability, as did replacement of citrate with acetate buffer, as shown in Table 2.

Table 2. Pseudo first order rate constants for vincristine degradation at approx. 1 mg/ml in various solutions at 65°C

Formulation	K_{obs} x $10^7 s^{-1}$
Citrate buffer*	28.0
	33.5
Citrate buffer, mannitol (100 mg/ml)	19.7
Acetate buffer*	19.0
Acetate buffer, mannitol (100 mg/ml)	10.5
Vincasar®	5.97
	6.36
	5.55

*The pH for buffer used in above experiments was about 4.6 ± 0.1. The buffer concentration was 300 mM for citrate, 400 mM for acetate. The reactions were carried out at 65°C and pseudo first order rate constants were obtained according to the equation of $\ln[vinc]_t = k_{obs}t + C$.

The data in Table 2 demonstrate that vincristine is much less stable in citrate buffer, even in the presence of mannitol, than when it is when present in 100 mg/ml mannitol alone, as supplied in its commercial form termed Vincasar®. As shown, the rates of vincristine degradation are approximately 3-5 fold faster in citrate buffer (under various conditions) as compared to Vincasar®. The stability data shown in Tables 1 and 2 were obtained using vincristine sulfate. However, as the vincristine salt will be fully dissociated in solution, and the degradation pathway is via deformylation of the vindoline moiety, it would be expected that similar degradation rates would be observed for other vincristine salt forms.

5. In light of the data presented above, I submit that the kit formats disclosed by Mehlhorn are unsuitable to provide a liposomal vincristine product with an acceptable shelf-life. The kits described by Mehlhorn require that the vincristine is present in either the vial containing the liposomes or the alkaline buffer vial. Vincristine is unstable in alkaline solutions and hence would be rapidly degraded in the buffer vial. Accordingly, if, for the purpose of argument, it was considered that Mehlhorn provided a motivation to provide liposomal vincristine in a kit format, it would have been obvious to include the drug within the liposome vial (as suggested by Mehlhorn) as the liposomes are suspended in citrate buffer pH 4.0, and vincristine is known to exhibit optimal stability at pH 3.5-5.5 (Vendrig *et al.*, International Journal of Pharmaceutics, 50 (1989) 189-196). What was not known in the art prior to the filing of the instant application is that in this citrate buffer, vincristine would be degraded at approximately the same rate as if encapsulated in the liposomes. Accordingly, such a kit format would have the same limited shelf-life as the fully loaded liposomes. It is only by providing the vincristine sulfate in a separate vial, in a solution suited to drug stability, that a commercially acceptable shelf-life is achieved. Thus, the presently claimed kits, which comprise three components: (1) liposomes; (2) buffer; and (3) drug in a solution suited to drug stability; provide unexpected advantages over the kit formats described by Mehlhorn.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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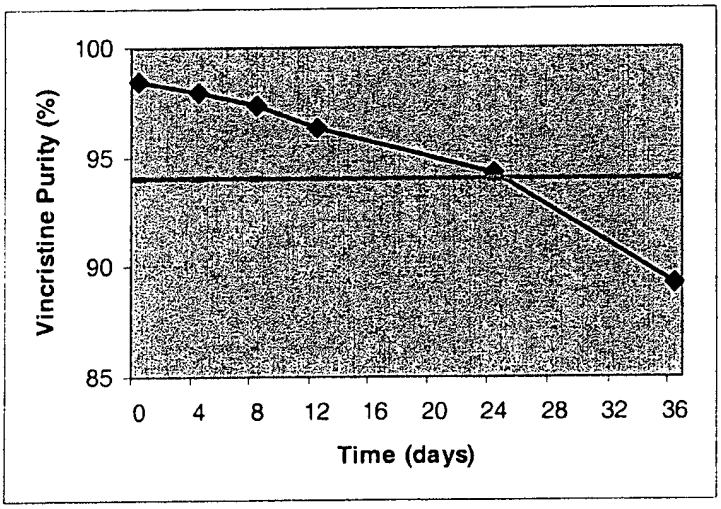

Figure 1